

## EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	25	(gomez adj robert.inv.)	US-PGPUB; USPAT	OR	OFF	2007/03/15 21:36
L2	4	(jolly adj samson.inv.)	US-PGPUB; USPAT	OR	OFF	2007/03/15 21:36
L3	22	(lim adj john.inv.)	US-PGPUB; USPAT	OR	OFF	2007/03/15 21:37
L4	40	(su adj dai-shi.inv.)	US-PGPUB; USPAT	OR	OFF	2007/03/15 21:37

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Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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L3	22	(lim adj john.inv.)	US-PGPUB; USPAT	OR	OFF	2007/03/15 21:37
L4	40	(su adj dai-shi.inv.)	US-PGPUB; USPAT	OR	OFF	2007/03/15 21:37

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TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	OCT 23	The Derwent World Patents Index suite of databases on STN has been enhanced and reloaded
NEWS	4	OCT 30	CHEMLIST enhanced with new search and display field
NEWS	5	NOV 03	JAPIO enhanced with IPC 8 features and functionality
NEWS	6	NOV 10	CA/CAPLUS F-Term thesaurus enhanced
NEWS	7	NOV 10	STN Express with Discover! free maintenance release Version 8.01c now available
NEWS	8	NOV 20	CA/CAPLUS to MARPAT accession number crossover limit increased to 50,000
NEWS	9	DEC 01	CAS REGISTRY updated with new ambiguity codes
NEWS	10	DEC 11	CAS REGISTRY chemical nomenclature enhanced
NEWS	11	DEC 14	WPIDS/WPINDEX/WPIX manual codes updated
NEWS	12	DEC 14	GBFULL and FRFULL enhanced with IPC 8 features and functionality
NEWS	13	DEC 18	CA/CAPLUS pre-1967 chemical substance index entries enhanced with preparation role
NEWS	14	DEC 18	CA/CAPLUS patent kind codes updated
NEWS	15	DEC 18	MARPAT to CA/CAPLUS accession number crossover limit increased to 50,000
NEWS	16	DEC 18	MEDLINE updated in preparation for 2007 reload
NEWS	17	DEC 27	CA/CAPLUS enhanced with more pre-1907 records
NEWS	18	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS	19	JAN 16	CA/CAPLUS Company Name Thesaurus enhanced and reloaded
NEWS	20	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS	21	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS	22	JAN 22	CA/CAPLUS updated with revised CAS roles
NEWS	23	JAN 22	CA/CAPLUS enhanced with patent applications from India
NEWS	24	JAN 29	PHAR reloaded with new search and display fields
NEWS	25	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS	26	FEB 13	CASREACT coverage to be extended
NEWS	27	FEB 15	PATDPASPC enhanced with Drug Approval numbers
NEWS	28	FEB 15	RUSSIAPAT enhanced with pre-1994 records
NEWS	29	FEB 23	KOREAPAT enhanced with IPC 8 features and functionality
NEWS	30	FEB 26	MEDLINE reloaded with enhancements
NEWS	31	FEB 26	EMBASE enhanced with Clinical Trial Number field
NEWS	32	FEB 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS	33	FEB 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS	34	FEB 26	CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
NEWS	35	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format

Updated Search

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NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT  
MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

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NEWS LOGIN Welcome Banner and News Items  
NEWS IPC8 For general information regarding STN implementation of IPC 8  
NEWS X25 X.25 communication option no longer available

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FILE 'HOME' ENTERED AT 15:11:04 ON 15 MAR 2007

=> file reg		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 15:11:13 ON 15 MAR 2007  
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DICTIONARY FILE UPDATES: 14 MAR 2007 HIGHEST RN 926494-79-3

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experimental property data in the original document. For information  
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> file hcaplus		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	0.45	0.66

FILE 'HCAPLUS' ENTERED AT 15:11:17 ON 15 MAR 2007

Updated Search

10565040

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FILE COVERS 1907 - 15 Mar 2007 VOL 146 ISS 12  
FILE LAST UPDATED: 14 Mar 2007 (20070314/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s aminocyclopropanecarboxamide
      9 AMINOCYCLOPROPANECARBOXAMIDE
      1 AMINOCYCLOPROPANECARBOXAMIDES
L1      9 AMINOCYCLOPROPANECARBOXAMIDE
        (AMINOCYCLOPROPANECARBOXAMIDE OR AMINOCYCLOPROPANECARBOXAMIDES
        )
```

```
=> s l1 and bradyknin antagonist?
      0 BRADYKNIN
      244459 ANTAGONIST?
      0 BRADYKNIN ANTAGONIST?
        (BRADYKNIN(W)ANTAGONIST?)
L2      0 L1 AND BRADYKNIN ANTAGONIST?
```

```
=> s l1 and bradykinin
      18069 BRADYKININ
      199 BRADYKININS
      18100 BRADYKININ
        (BRADYKININ OR BRADYKININS)
L3      2 L1 AND BRADYKININ
```

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=> s l3 and antagonist?
      244459 ANTAGONIST?
L4      2 L3 AND ANTAGONIST?
```

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=> s l4 and review/dt
      2010319 REVIEW/DT
L5      0 L4 AND REVIEW/DT
```

```
=> d l4, ibib abs hitstr, 1-2
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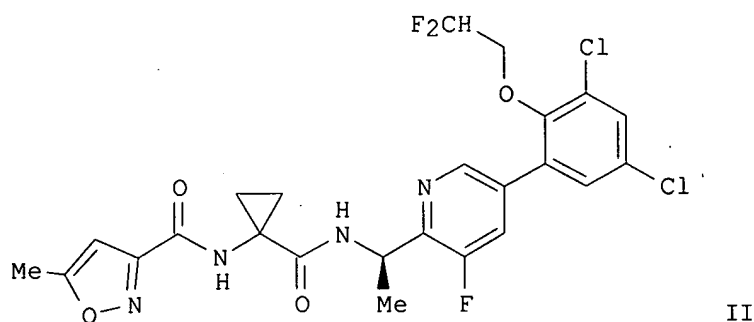
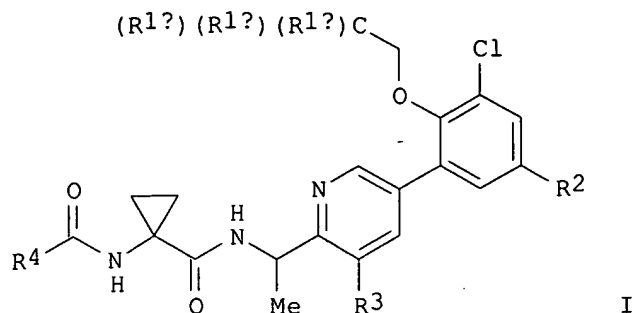
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L4  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:  2005:1004708  HCAPLUS
DOCUMENT NUMBER:   143:306182
TITLE:             Preparation of 1-aminocyclopropane-1-carboxamide
                   derivatives as bradykinin B1
```

Updated Search

10565040

antagonists  
INVENTOR(S): Bock, Mark G.; Feng, Dong-Mei; Kuduk, Scott  
PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
SOURCE: PCT Int. Appl., 40 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005085198	A2	20050915	WO 2005-US6230	20050225
WO 2005085198	A3	20051124		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2005219836	A1	20050915	AU 2005-219836	20050225
CA 2557858	A1	20050915	CA 2005-2557858	20050225
EP 1723143	A2	20061122	EP 2005-714101	20050225
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LV			
CN 1926136	A	20070307	CN 2005-80006734	20050225
PRIORITY APPLN. INFO.:			US 2004-549379P	P 20040302
			WO 2005-US6230	W 20050225
OTHER SOURCE(S):	MARPAT 143:306182			
GI				



AB Title compds. I [wherein R1a, R1b, R1c = H or F; R2 = H or Cl; R3 = Cl or F; R4 = (un)substituted (cyclo)alkyl, aryl or heterocycle, or pharmaceutically acceptable salts thereof] were prepared as antagonists or inverse agonists of bradykinin receptors, especially as antagonists of bradykinin receptor B1. For instance, II was synthesized by acylation of dihydrochloride salt of the corresponding cyclopropanamine with 5-methylisoxazole-3-carbonyl chloride in the presence of DIPEA. I exhibited affinity for the B1 receptor with IC50 values of < 5 $\mu$ M. Therefore, I and their pharmaceutical compns. (examples given) are useful in the treatment or prevention of symptoms such as pain and inflammation associated with the bradykinin B1 pathway.

L4 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:158641 HCAPLUS

DOCUMENT NUMBER: 142:261546

TITLE: Preparation of sulfonyl substituted N-(biarylmethyl) aminocyclopropanecarboxamides as bradykinin B1 antagonists or inverse agonists

INVENTOR(S): Anthony, Neville J.; Gomez, Robert; Jolly, Samson M.; Lim, John Jin; Su, Dai-shi

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 57 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.

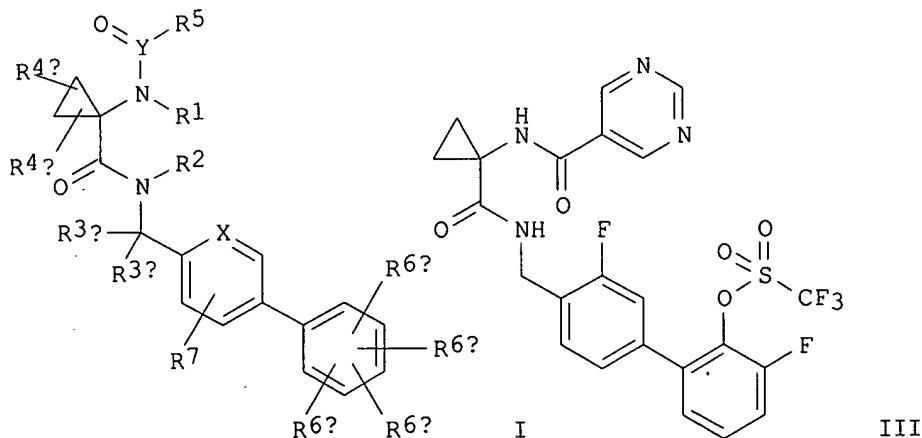
KIND

DATE

APPLICATION NO.

DATE

WO 2005016886	A1	20050224	WO 2004-US25037	20040803
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004265300	A1	20050224	AU 2004-265300	20040803
CA 2534188	A1	20050224	CA 2004-2534188	20040803
EP 1654232	A1	20060510	EP 2004-779955	20040803
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1832922	A	20060913	CN 2004-80022661	20040803
JP 2007501790	T	20070201	JP 2006-522671	20040803
US 2006247229	A1	20061102	US 2006-565040	20060118
PRIORITY APPLN. INFO.:			US 2003-493146P	P 20030807
			US 2003-493257P	P 20030807
			WO 2004-US25037	W 20040803
OTHER SOURCE(S):			MARPAT 142:261546	
GI				



AB N-(Sulfonyloxybiarylmethyl)aminocyclopropanecarboxamide derivs.  
 (I) [R1, R2 = H, C1-4 alkyl; R3a, R3b = H, (un)substituted C1-4 alkyl; R4a, R4b = H, halogen, (un)substituted C1-4 alkyl; or R4a and R4b together with the carbon atom to which they are both attached form an (un)substituted exocyclic methylene; R5 = each (un)substituted C1-6 alkyl, C3-8 cycloalkyl, C3-6 alkynyl, C2-6 alkenyl, (CH2)*k*-aryl, (CH2)*k*-heterocycle; R6a = -OSO2R8, -NR8aSO2R9, -C(R8b)(R8c)SO2R9; R6b, R6c, R6d = H, halogen, OSO2R8, (un)substituted C1-4 alkyl, cyano, nitro, ORa, CO2Ra, or when attached to adjacent carbon atoms R6c and R6d together with the carbon atoms to which they are attached form a 5- to 8-membered saturated or unsatd. ring; R7 = H, halogen, cyano, nitro, ORa, CO2Ra, C(O)NRbRc, (un)substituted C1-4 alkyl; R8 = H, each (un)substituted C1-4



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alkyl, (CH<sub>2</sub>)<sub>k</sub>-aryl, or NH<sub>2</sub>; R<sub>8a</sub>, R<sub>8b</sub>, R<sub>8c</sub> = H, (un)substituted C1-4 alkyl; or when R<sub>6a</sub> and R<sub>6b</sub> are attached to adjacent atoms, R<sub>8a</sub> and R<sub>6b</sub> together complete 5- or 6-membered ring; R<sub>9</sub> = each (un)substituted C1-4 alkyl, aryl, or (CH<sub>2</sub>)<sub>k</sub>-aryl; R<sub>a</sub>, R<sub>b</sub>, R<sub>c</sub> = H, each C1-4 alkyl or Ph, C3-6 cycloalkyl; or NR<sub>b</sub>R<sub>c</sub> together forms a cyclic imide or a 4-, 5-, or 6-membered ring optionally containing an addnl. heteroatom selected from N, O, and S; X = CH, N; Y = C, S(O); k = 0, 1, 2]. These compds. are bradykinin B1 antagonists or inverse agonists useful in the treatment or prevention of symptoms such as pain and inflammation associated with the bradykinin B1 pathway. Thus, N-[1-[[[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]amino]carbonyl]cyclopropyl]pyrimidine-5-carboxamide was coupled with 1-bromo-3-fluoro-2-methoxybenzene in the presence of tetrakis(triphenylphosphine)palladium(0) and potassium phosphate at 110° for 16 h to give N-[1-[[[(3,3'-difluoro-2'-methoxy-1,1'-biphenyl-4-yl)methyl]amino]carbonyl]cyclopropyl]pyrimidine-5-carboxamide which was treated with boron tribromide in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 48 h to give N-[1-[[[(3,3'-difluoro-2'-hydroxy-1,1'-biphenyl-4-yl)methyl]amino]carbonyl]cyclopropyl]pyrimidine-5-carboxamide (II). II was stirred with trifluoromethanesulfonic anhydride in the presence of Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 2 h to give

3,3'-difluoro-4'-[[[1-[(pyrimidin-5-ylcarbonyl)amino]cyclopropyl]carbonyl]amino]methyl]-1,1'-biphenyl-2-yl trifluoromethanesulfonate (III).

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s bradykinin () antagonist?

18069 BRADYKININ  
199 BRADYKININS  
18100 BRADYKININ  
(BRADYKININ OR BRADYKININS)  
244459 ANTAGONIST?

L6 650 BRADYKININ (W) ANTAGONIST?

=> s L6 and pain

49104 PAIN  
1222 PAINS  
49922 PAIN  
(PAIN OR PAINS)

L7 77 L6 AND PAIN

=> s L7 and review/dt

2010319 REVIEW/DT

L8 12 L7 AND REVIEW/DT

=> d L8, ibib abs hitstr, 1-12

L8 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:1220368 HCAPLUS

DOCUMENT NUMBER: 146:54563

TITLE: Pharmacologic targets and prototype therapeutics in the kallikrein-kinin system: bradykinin receptor agonists or antagonists

AUTHOR(S): Sharma, J. N.; Al-Sherif, G. J.

CORPORATE SOURCE: Department of Applied Therapeutics, Faculty of Pharmacy, Health Sciences Centre, Kuwait University, Safat, 13110, Kuwait

Updated Search

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SOURCE: TheScientificWorld (2006), 6(Oct.), 1247-1261  
CODEN: THESAS; ISSN: 1532-2246  
URL: <http://www.thescientificworld.com/headeradmin/upload/2006.01.226.pdf>  
PUBLISHER: TheScientificWorld, Inc.  
DOCUMENT TYPE: Journal; General Review; (online computer file)  
LANGUAGE: English

AB A review. The kallikrein-kinin system (KKS) is a complex system produced in various organs. This system includes kininogen (precursor for kinin), kallikreins, and pharmacol. active bradykinin (BK), which is considered to be proinflammatory and/or cardioprotective. It is a proinflammatory polypeptide that is involved in many pathol. conditions and can cause pain, inflammation, increased vascular permeability, vasodilation, contraction of various smooth muscles, as well as cell proliferation. On the other hand, it has been shown that BK has cardioprotective effects, as all components of KKS are located in the cardiac muscles. Numerous observations have indicated that decreased activity of this system may lead to cardiovascular diseases, such as hypertension, cardiac failure, and myocardial infarction. BK acts on two receptors, B1 and B2, which are linked physiol. through their natural stimuli and their common participation in a variety of inflammatory responses. Recently, numerous BK antagonists have been developed in order to treat several diseases that are due to excessive BK formation. Although BK has many beneficial effects, it has been recognized to have some undesirable effects that can be reversed with BK antagonists. In addition, products of this system have multiple interactions with other important metabolic pathways, such as the renin-angiotensin system.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:382377 HCAPLUS  
DOCUMENT NUMBER: 141:16720  
TITLE: Bradykinin antagonists: discovery and development  
AUTHOR(S): Stewart, John M.  
CORPORATE SOURCE: Department of Biochemistry, University of Colorado Medical School, Denver, CO, 80262, USA  
SOURCE: Peptides (New York, NY, United States) (2004), 25(3), 527-532  
CODEN: PPTDD5; ISSN: 0196-9781  
PUBLISHER: Elsevier Science Inc.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Practical bradykinin antagonists were discovered in 1984 by Vavrek and Stewart and reported in "Peptides." At that time there was already much evidence for involvement of bradykinin in inflammation and pain, so the specific, competitive antagonists were widely accepted and applied. The key to conversion of bradykinin into an antagonist was replacement of the proline residue at position 7 with a d-aromatic amino acid. Other modifications converted the initial weak antagonists into modern peptides which are totally resistant to all degrading enzymes, are orally available, and have been used in clin. trials. Non-peptide bradykinin antagonists have also been developed.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Updated Search

10565040

L8 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:246324 HCAPLUS  
DOCUMENT NUMBER: 139:270066  
TITLE: Topical and peripherally acting analgesics  
AUTHOR(S): Sawynok, Jana  
CORPORATE SOURCE: Department of Pharmacology, Dalhousie University,  
Halifax, NS, Can.  
SOURCE: Pharmacological Reviews (2003), 55(1), 1-20  
CODEN: PAREAQ; ISSN: 0031-6997  
PUBLISHER: American Society for Pharmacology and Experimental  
Therapeutics  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Acute nociceptive, inflammatory, and neuropathic pain all depend to some degree on the peripheral activation of primary sensory afferent neurons. The localized peripheral administration of drugs, such as by topical application, can potentially optimize drug concns. at the site of origin of the pain, while leading to lower systemic levels and fewer adverse systemic effects, fewer drug interactions, and no need to titrate doses into a therapeutic range compared with systemic administration. Primary sensory afferent neurons can be activated by a range of inflammatory mediators such as prostanoids, bradykinin, ATP, histamine, and serotonin, and inhibiting their actions represents a strategy for the development of analgesics. Peripheral nerve endings also express a variety of inhibitory neuroreceptors such as opioid,  $\alpha$ -adrenergic, cholinergic, adenosine and cannabinoid receptors, and agonists for these receptors also represent viable targets for drug development. At present, topical and other forms of peripheral administration of nonsteroidal anti-inflammatory drugs, opioids, capsaicin, local anesthetics, and  $\alpha$ -adrenoceptor agonists are being used in a variety of clin. states. There also are some clin. data on the use of topical antidepressants and glutamate receptor antagonists. There are preclin. data supporting the potential for development of local formulations of adenosine agonists, cannabinoid agonists, cholinergic ligands, cytokine antagonists, bradykinin antagonists, ATP antagonists, biogenic amine antagonists, neuropeptide antagonists, and agents that alter the availability of nerve growth factor. Given that activation of sensory neurons involves multiple mediators, combinations of agents targeting different mechanisms may be particularly useful. Topical analgesics represent a promising area for future drug development.

REFERENCE COUNT: 362 THERE ARE 362 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L8 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:148931 HCAPLUS  
DOCUMENT NUMBER: 136:145353  
TITLE: Bradykinin antagonist: current  
status and perspective  
AUTHOR(S): Hirayama, Yoshitaka; Kayakiri, Hiroshi  
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa  
Pharmaceutical Co., Ltd., Yodogawa-ku, Osaka,  
532-8514, Japan  
SOURCE: Nippon Yakurigaku Zasshi (2002), 119(1), 45-53  
CODEN: NYKZAU; ISSN: 0015-5691  
PUBLISHER: Nippon Yakuri Gakkai  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: Japanese

AB A review. The kallikrein-kinin system plays an important role in many

Updated Search

physiol. and pathophysiol. conditions such as homeostasis of circulation, inflammation/allergy, pain, shock, etc. Two types of kinin receptor are known, bradykinin (BK) B1 receptor and BK B2 receptor. B2 receptors are constitutively expressed and mediate most physiol. actions of kinins, whereas B1 receptors are highly inducible upon inflammatory stimulation or tissue injury, suggesting that they are involved in inflammation and/or nociception. Only three peptide type B2 antagonists, NPC 567, CP-0127, and HOE-140, have been evaluated in clin. studies so far, and some beneficial effects of B2 antagonists have been shown for rhinitis, asthma, systemic inflammatory response syndrome/sepsis, and brain injury. However, the results were less convincing than expected. Now several potent and orally active nonpeptide B2-receptor antagonists have been found, which are expected to overcome the weak point of the peptide type antagonists and clarify the therapeutic potential of the B2-receptor antagonist for novel indications as well as those mentioned above. As for B1 receptors, no antagonist has been tested in a clin. trial. The important role of B1 receptors is just being elucidated by use of peptide type antagonists or B1 receptor gene knockout mice. The further development of newer B1 antagonists and clin. evaluation is desired.

L8 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:298214 HCAPLUS

DOCUMENT NUMBER: 134:294182

TITLE: Inflammation-allergy and prostanoids. (1) Prostanoids in experimental inflammatory reaction

AUTHOR(S): Ueno, Akinori; Ohishi, Sachiko

CORPORATE SOURCE: Dep. Pharmacol., Sch. Pharm. Sci., Kitasato Univ., 5-9-1 Shirokane, Minato-ku, Tokyo, 108-8642, Japan

SOURCE: Nippon Yakurigaku Zasshi (2001), 117(4), 255-261

CODEN: NYKZAU; ISSN: 0015-5691

PUBLISHER: Nippon Yakuri Gakkai

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese

AB A review with 22 refs. It is known that prostaglandins (PGs) modify the inflammatory reaction in concert with other biol. active mediators. However, characteristics of these interactions or modulating actions have not yet been clarified well. Recently, the production of mice with specific receptor deficiencies by using the gene targeting procedure for PG receptors has accelerated elucidation of the roles of PGs through correlation of their phenotypes and exptl. features. Here I discuss roles of PGs in exptl. paw edema, the writhing reaction of a pain model, and regulation of cytokine formation, as determined using some PG-receptor-deficient mice. From the experiment of carrageenin-induced paw edema in IP receptor-deficient mice, with an indomethacin or bradykinin antagonist, we conclude that bradykinin initially induces paw swelling and then stimulates the release PGI<sub>2</sub>, which in turn enhances the swelling with bradykinin. By comparing the writhing responses in IP-deficient and wild-type mice, we found that PGI<sub>2</sub> is a main mediator for this pain reaction. However, in the LPS-pretreated mice, not only PGI<sub>2</sub> but also other PGs produced by COX-2 may be involved in pain induction. Formation of TNF $\alpha$  and IL-10 was modified with PGI<sub>2</sub> or PGE<sub>2</sub>; the formation of TNF $\alpha$  was down-regulated by the stimulation via IP-, EP2- or EP4 receptor, but that of IL-10 was up-regulated by these receptors, resulting in an anti-inflammatory effect.

L8 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:584130 HCAPLUS

DOCUMENT NUMBER: 133:246693

10565040

TITLE: Bradykinin antagonists: new opportunities  
AUTHOR(S): Bock, Mark G.; Longmore, Jeanette  
CORPORATE SOURCE: Merck Research Laboratories, West Point, PA, 19486, USA  
SOURCE: Current Opinion in Chemical Biology (2000), 4(4), 401-406  
CODEN: COCBF4; ISSN: 1367-5931  
PUBLISHER: Elsevier Science Ltd.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
AB A review with 40 refs. The pro-inflammatory, pain producing, and cardiovascular effects of bradykinin B2 receptor activation are well characterized. Bradykinin B1 receptors also produce inflammation and pain. Therefore, antagonists are expected to be anti-inflammatory/analgesic drugs. Other exploitable clin. opportunities may exist. The newly discovered non-peptide B2 receptor antagonists and the equivalent B1 receptor pharmacol. agents, which are in the pipeline, are suitable preclin. tools to properly evaluate potential utilities.  
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2000:324230 HCAPLUS  
DOCUMENT NUMBER: 133:83738  
TITLE: Kallikrein-kinin system in acute pancreatitis: potential of B2-bradykinin antagonists and kallikrein inhibitors  
AUTHOR(S): Griesbacher, Thomas  
CORPORATE SOURCE: Department of Experimental and Clinical Pharmacology, University of Graz, Graz, A-8010, Austria  
SOURCE: Pharmacology (2000), 60(3), 113-120  
CODEN: PHMGBN; ISSN: 0031-7012  
PUBLISHER: S. Karger AG  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
AB A review with 36 refs. The development of selective antagonists for bradykinin B2 receptors has greatly advanced research on the role of the kallikrein-kinin system in acute pancreatitis. Kinins released during the course of the inflammatory injury are the major cause of the vascular symptoms, i.e. pancreatic edema formation and its consequences, such as hemoconcn., hypovolemia and hypotension. Kinins are also involved in the accumulation of potentially cytotoxic factors in the pancreatic tissue. However, treatment with B2 antagonists must begin prior to the formation of pancreatic edema to inhibit or attenuate the vascular effects. Visceral pain as a possible target symptom for treatment with B2 antagonists at later time points is suggested by the B2 receptor-mediated activation of nociceptive afferents.  
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 1997:492671 HCAPLUS  
DOCUMENT NUMBER: 127:170901  
TITLE: Nonconventional analgesics: bradykinin antagonists  
AUTHOR(S): Elguero, Jose; Rozas, Isabel  
CORPORATE SOURCE: Instituto de Quimica Medica (C. S. I. C.), Spain  
SOURCE: Anales de la Real Academia de Farmacia (1997), 63(1),

Updated Search

173-190

CODEN: ARAFAY; ISSN: 0034-0618

PUBLISHER:

Real Academia de Farmacia

DOCUMENT TYPE:

Journal; General Review

LANGUAGE:

Spanish

AB A review with 34 refs. Bradykinin and kallidin, "kinins", are generated by the activity of kallikreins (proteolytic enzymes) on kininogens. Kinins elicit pathophysiol. responses including pain and hyperalgesia. Kinins receptors are classified according to the relative potencies of agonist and antagonists. Regoli and Barabe proposed two subtypes of receptors, B1 and B2. Hundreds of agonists analogs of bradykinin were prepared before the first antagonist compds. appeared. Synthetic efforts have been oriented towards peptidic analogs until few years ago when the search of non-peptidic antagonists started. The distribution of receptor B1 in the human being is very limited and probably this subtype plays an unimportant role on human diseases. Two generation of peptidic antagonists of the B2 receptor have been developed. The second generation has compds. two orders of magnitude more potent as analgesics than the first generation ones and the most important derivative was icatibant. The first non-peptidic antagonist of the B2 receptor, described in 1993, has two phosphonium cations separated by a modified amino acid. Many derivs. of this dication have been prepared. Another non-peptidic compound antagonist of B2 is the natural product Martinelline. Mol. modeling and QSAR studies have been carried out on bradykinin as well as on its antagonists.

L8 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:873978 HCAPLUS

DOCUMENT NUMBER: 123:275023

TITLE: Kinin receptor antagonists: unique probes in basic and clinical research

AUTHOR(S): Wirth, Klaus J.; Heitsch, Holger; Schoelkens, Bernhard A.

CORPORATE SOURCE: HR PGU Cardiovascular Agents, Frankfurt am Main, D-65926, Germany

SOURCE: Canadian Journal of Physiology and Pharmacology (1995), 73(7), 797-804

CODEN: CJPPA3; ISSN: 0008-4212

PUBLISHER: National Research Council of Canada

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with  $\approx$  50 refs. The availability of potent and stable bradykinin antagonists has had a tremendous impact on kinin research. This article reviews the current status of research on kinin antagonists, describes their chemical properties, and delineates recent advances that have occurred with the advent of the second generation of kinin antagonists. The data collected with these antagonists support the assumption that kinins are implicated in inflammation and tissue injury as endogenous agents. Their importance, however, is not limited to the role as mediators of tissue injury and inflammation, as kinin antagonists have enabled the identification of kinins as potential endogenous cardioprotective substances, also contributing to the effects of angiotensin converting enzyme inhibitors. Clin. studies are currently being performed in asthma, postoperative pain, anaphylactoid reactions during low d. lipoprotein apheresis, systemic inflammation response syndrome, and suspected sepsis, head injury, and hantavirus infections to investigate the utility of kinin antagonists as therapeutic agents.

10565040

L8 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1993:401036 HCAPLUS  
DOCUMENT NUMBER: 119:1036  
TITLE: Therapeutic prospects of bradykinin receptor antagonists  
AUTHOR(S): Sharma, J. N.  
CORPORATE SOURCE: Sch. Med. Sci., Univ. Sains Malaysia, Kubang Kerian, 16150, Malay.  
SOURCE: General Pharmacology (1993), 24(2), 267-74  
CODEN: GEPHDP; ISSN: 0306-3623  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review with 77 refs. Bradykinin (BK) and related kinins may act on 4 types of receptors designated as B1, B2, B3, and B4. It seems that the B2 receptors are most commonly found in various vascular and non-vascular smooth muscles, whereas B1 receptors are formed in vitro during trauma, and injury, and are found in bone tissues. These BK receptors are involved in the regulations of various physiol. and pathol. processes. The mode of kinin actions are based upon the interactions between the kinin and their specific receptors, which can led to activation of several second-messenger systems. Numerous BK receptor antagonists have been synthesized with prime aim to treat diseases caused by excessive kinin production. These diseases are RA, inflammatory diseases of the bowel, asthma, rhinitis and sore throat, allergic reactions, pain, inflammatory skin disorders, endotoxin and anaphylactic shock and coronary heart diseases. On the other hand, BK receptor antagonists could be contraindicated in hypertension, since these drugs may antagonize the antihypertensive therapy and/or may trigger the hypertensive crisis. It is worth suggesting that the BK receptor agonists might be useful antihypertensive drugs.

L8 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1991:506210 HCAPLUS  
DOCUMENT NUMBER: 115:106210  
TITLE: Nonopioid molecular signaling mechanisms involved in nociception and antinociception  
AUTHOR(S): Dray, A.; Wood, J. N.  
CORPORATE SOURCE: Sandoz Inst. Med. Res., London, WC1D 6BN, UK  
SOURCE: Life Sciences Research Report (1991), 49(Towards New Pharmacother. Pain), 21-34  
CODEN: LSRPD8; ISSN: 0340-8132  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review with 32 refs. Studies of the sensitization and activation of nociceptive sensory neurons have identified some of the mol. mechanisms that underlie the primary events which may result in the sensation of pain. Nociceptive sensory neurons are activated by several endogenous ligands, either through ligand-gated ion channels (e.g., 5-HT, ATP) or through intracellular second messengers (e.g., bradykinin); neuronal excitability is regulated by a host of eicosanoids, cytokines, and neuropeptides, by as yet ill-defined mechanisms. Intracellular second messengers which alter the phosphorylation states of ion channels and pumps are likely to contribute to these actions. Novel analgesic drugs that act peripherally may thus be targeted at ion channels and receptors (e.g., bradykinin antagonists), at second message levels, or as selective inhibitors of specific kinases (e.g., calphostin). Recently, novel analgesic drugs based on the selective excitotoxin capsaicin have also been developed. The mol. mechanisms underlying these events are discussed.

Updated Search

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L8 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 1991:421390 HCAPLUS  
DOCUMENT NUMBER: 115:21390  
TITLE: Bradykinin antagonists in  
pain and inflammation  
AUTHOR(S): Steranka, Larry R.; Burch, Ronald M.  
CORPORATE SOURCE: Nova Pharm. Corp., Baltimore, MD, USA  
SOURCE: Inflammatory Disease and Therapy (1990), 5(Bradykinin  
Antagonists), 191-211  
CODEN: IDITE8; ISSN: 1047-5028  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
AB A review with 74 refs. discussing the effects of peptide  
bradykinin antagonists and certain kallikrein inhibitors  
on models of inflammation and pain.

=> d his

(FILE 'HOME' ENTERED AT 15:11:04 ON 15 MAR 2007)

FILE 'REGISTRY' ENTERED AT 15:11:13 ON 15 MAR 2007

FILE 'HCAPLUS' ENTERED AT 15:11:17 ON 15 MAR 2007

L1 9 S AMINOCYCLOPROPANECARBOXAMIDE  
L2 0 S L1 AND BRADYKNIN ANTAGONIST?  
L3 2 S L1 AND BRADYKININ  
L4 2 S L3 AND ANTAGONIST?  
L5 0 S L4 AND REVIEW/DT  
L6 650 S BRADYKININ () ANTAGONIST?  
L7 77 S L6 AND PAIN  
L8 12 S L7 AND REVIEW/DT

=> s 16 and postherpetic () neuropathy?

375 POSTHERPETIC

12604 NEUROPATHY?

1 POSTHERPETIC (W) NEUROPATHY?

L9 0 L6 AND POSTHERPETIC (W) NEUROPATHY?

=> s 16 and osteoarthritis?

8812 OSTEOARTHRITIS?

L10 6 L6 AND OSTEOARTHRITIS?

=> s 110 and review/dt

2010319 REVIEW/DT

L11 0 L10 AND REVIEW/DT

=> s 16 and dental () pain?

48023 DENTAL

6 DENTALS

48024 DENTAL

(DENTAL OR DENTALS)

149167 PAIN?

201 DENTAL (W) PAIN?

L12 0 L6 AND DENTAL (W) PAIN?

Updated Search



10565040

=> d his

(FILE 'HOME' ENTERED AT 19:10:40 ON 14 MAR 2007)

FILE 'REGISTRY' ENTERED AT 19:10:46 ON 14 MAR 2007

L1 STRUCTURE UPLOADED

L2 15 S L1

L3 347 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 19:16:20 ON 14 MAR 2007

L4 7 S L3

L5 0 S L4 AND NEVILLE, A?/AU

L6 1 S L4 AND GOMEZ, R?/AU

L7 6 S L4 NOT L6

L8 0 S L7 AND JOLLY, S?/AU

L9 0 S L7 AND LIM, J?/AU

L10 2 S L7 AND SU, D?/AU

L11 4 S L7 NOT L10

L12 0 S L11 AND ANTHONY, N?/AU

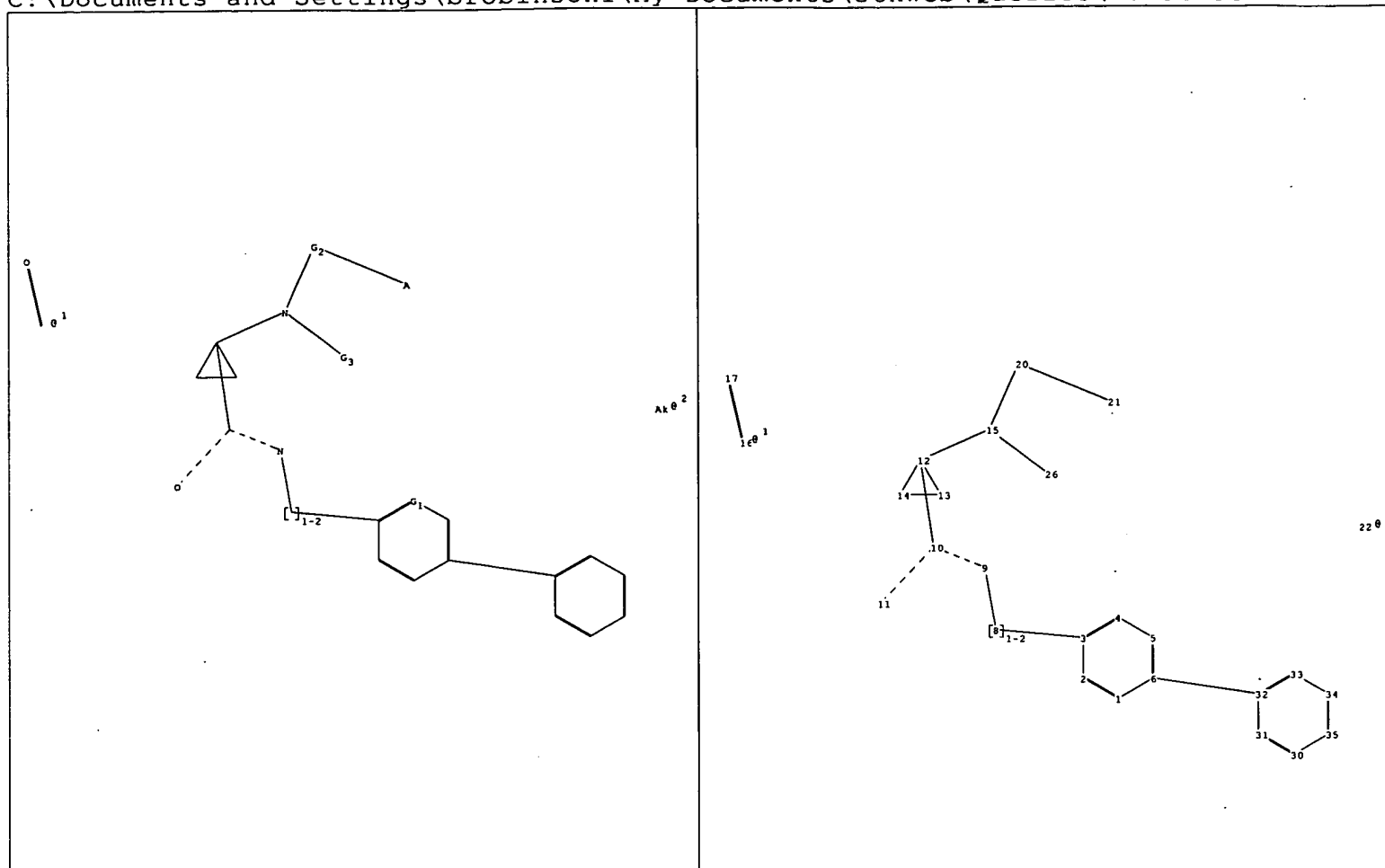
FILE 'CAOLD' ENTERED AT 19:19:31 ON 14 MAR 2007

=> s 13

L13 0 L3

=>

Updated Search



chain nodes :

8 9 10 11 15 16 17 20 21 22 26

ring nodes :

1 2 3 4 5 6 12 13 14 30 31 32 33 34 35

chain bonds :

3-8 6-32 8-9 9-10 10-11 10-12 12-15 15-20 15-26 16-17 20-21

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-14 13-14 30-31 30-35 31-32  
32-33 33-34 34-35

exact/norm bonds :

1-2 1-6 2-3 3-4 3-8 4-5 5-6 6-32 8-9 9-10 10-11 10-12 12-13  
12-14 12-15 13-14 15-20 15-26 16-17 20-21

normalized bonds :

30-31 30-35 31-32 32-33 33-34 34-35

isolated ring systems :

containing 1 : 12 :

G1:C,N

G2:SO2,[\*1]

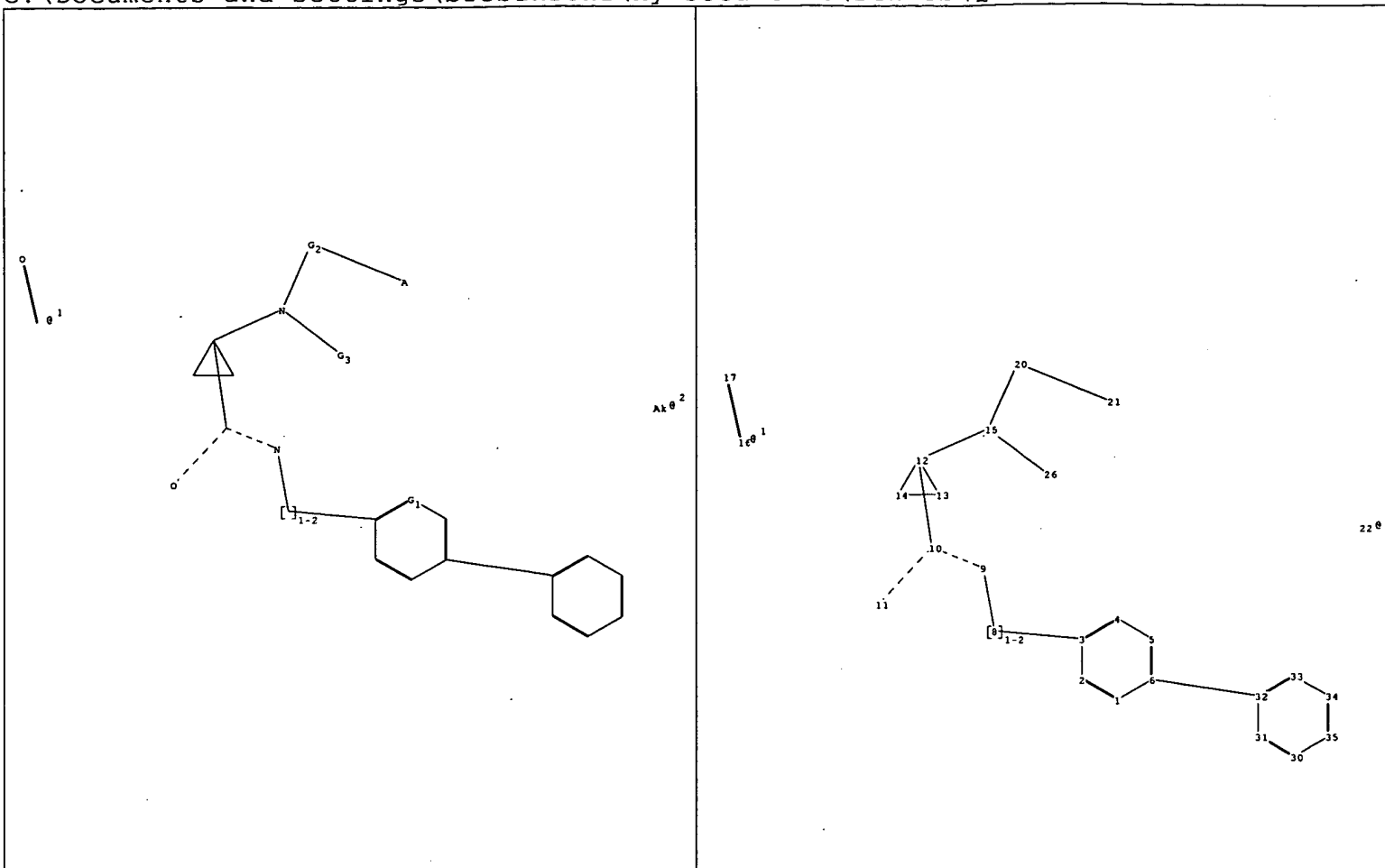
G3:H,[\*2]

Connectivity :

22:1 M minimum RC ring/chain

Match level :

1:Atom	2:Atom	3:Atom	4:Atom	5:Atom	6:Atom	8:CLASS	9:CLASS	10:CLASS
11:CLASS	12:Atom	13:Atom	14:Atom	15:CLASS	16:CLASS	17:CLASS	20:CLASS	
21:CLASS	22:CLASS	26:CLASS	30:Atom	31:Atom	32:Atom	33:Atom	34:Atom	
35:Atom								



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chain nodes :
  8  9 10 11 15 16 17 20 21 22 26
ring nodes :
  1  2  3  4  5  6 12 13 14 30 31 32 33 34 35
chain bonds :
  3-8 6-32 8-9 9-10 10-11 10-12 12-15 15-20 15-26 16-17 20-21
ring bonds :
  1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-14 13-14 30-31 30-35 31-32
  32-33 33-34 34-35
exact/norm bonds :
  1-2 1-6 2-3 3-4 3-8 4-5 5-6 6-32 8-9 9-10 10-11 10-12 12-13
  12-14 12-15 13-14 15-20 15-26 16-17 20-21
normalized bonds :
  30-31 30-35 31-32 32-33 33-34 34-35
isolated ring systems :
  containing 1 : 12 :

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G1:C,N
G2:SO2,[*1]
G3:H,[*2]

Connectivity :
  22:1 M minimum RC ring/chain
Match level :
  1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 8:CLASS 9:CLASS 10:CLASS
  11:CLASS 12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS 20:CLASS
  21:CLASS 22:CLASS 26:CLASS 30:Atom 31:Atom 32:Atom 33:Atom 34:Atom
  35:Atom

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PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

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NEWS	10	DEC 11	CAS REGISTRY chemical nomenclature enhanced
NEWS	11	DEC 14	WPIDS/WPINDEX/WPIX manual codes updated
NEWS	12	DEC 14	GBFULL and FRFULL enhanced with IPC 8 features and functionality
NEWS	13	DEC 18	CA/CAPLUS pre-1967 chemical substance index entries enhanced with preparation role
NEWS	14	DEC 18	CA/CAPLUS patent kind codes updated
NEWS	15	DEC 18	MARPAT to CA/CAPLUS accession number crossover limit increased to 50,000
NEWS	16	DEC 18	MEDLINE updated in preparation for 2007 reload
NEWS	17	DEC 27	CA/CAPLUS enhanced with more pre-1907 records
NEWS	18	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS	19	JAN 16	CA/CAPLUS Company Name Thesaurus enhanced and reloaded
NEWS	20	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS	21	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS	22	JAN 22	CA/CAPLUS updated with revised CAS roles
NEWS	23	JAN 22	CA/CAPLUS enhanced with patent applications from India
NEWS	24	JAN 29	PHAR reloaded with new search and display fields
NEWS	25	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS	26	FEB 13	CASREACT coverage to be extended
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NEWS	28	Feb 15	RUSSIAPAT enhanced with pre-1994 records
NEWS	29	Feb 23	KOREAPAT enhanced with IPC 8 features and functionality
NEWS	30	Feb 26	MEDLINE reloaded with enhancements
NEWS	31	Feb 26	EMBASE enhanced with Clinical Trial Number field
NEWS	32	Feb 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS	33	Feb 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS	34	Feb 26	CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases

Updated Search